IN THE SPECIFICATION:

On page 1, please replace the FIELD OF THE INVENTION section with the following:

One or more embodiments of the present invention relate to the formulation, methods of production, and methods of delivery, of perforated microstructures comprising an active agent.

On page 4, please delete the following paragraphs at lines 13-22:

Accordingly, it is an object of the present invention to provide methods and preparations that advantageously allow for the nasal or pulmonary administration of powders having relatively high fine particle fractions.

It is a further object of the present invention to provide stabilized preparations suitable for aerosolization and subsequent administration to the pulmonary air passages of a patient in need thereof.

It is yet another object of the present invention to provide powders that may be used to provide stabilized dispersions.

It is still a further object of the present invention to provide powders exhibiting relatively low cohesive forces that are compatible for use in dry powder inhalers.

Please delete the contents of the entire section entitled "SUMMARY OF THE INVENTION" on pages 6 to 12, and replace with the following:

SUMMARY

An inhaleable powder composition comprises a plurality of particulate microstructures, the microstructures comprising a structural matrix comprising an active agent, calcium and a phospholipid, wherein said microstructures have a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3.

In one version, the phospholipid comprises a gel to liquid crystal transition temperature of greater than 40°C.

Please replace the paragraph on page 11, lines 15 to page 12, line 2, with the following:

As discussed above, the present invention provides methods, systems and compositions that comprise perforated microstructures which, in preferred embodiments, may advantageously be used for the delivery of bioactive agents. More particularly, the present invention may provide for the delivery of bioactive agents to selected physiological target sites using perforated microstructure powders. In preferred embodiments, the bioactive agents are in a form for administration to at least a portion of the pulmonary air passages of a patient in need thereof. In particularly preferred embodiments, the disclosed perforated microstructure powders may be used in a dry state (e.g. as in a DPI) or in the form of a stabilized dispersion (e.g. as in a MDI, LDI or nebulizer formulation) to deliver bioactive agents to the nasal or pulmonary air passages of a patient. It will be appreciated that the perforated microstructures disclosed herein comprise a structural matrix that exhibits, defines or comprises voids, pores, defects, hollows, spaces, interstitial spaces, apertures, perforations or holes. The absolute shape (as opposed to the morphology) of the perforated microstructure is generally not critical and any overall configuration that provides the desired characteristics is contemplated as being within the scope of the invention. Accordingly, preferred embodiments can comprise approximately microspherical shapes. However, collapsed, deformed or fractured particulates are also compatible. With this caveat, it will further be appreciated that, particularly preferred embodiments of the invention comprise spray dried hollow, porous microspheres. In any case the disclosed powders of perforated microstructures provide several advantages including, but not limited to, increases in suspension stability, improved dispersibility, superior sampling characteristics, elimination of carrier particles and enhanced aerodynamics.

Please replace the paragraph on page 12, lines 3 – 10, with following:

Those skilled in the art will appreciate that many of these aspects are of particular use for dry powder inhaler applications. Unlike prior art formulations, the present invention provides unique methods and compositions to reduce cohesive forces between dry particles, thereby minimizing particulate aggregation which can result in an improved delivery efficiency. To that end, the present invention provides for the formation and use of perforated microstructures and delivery systems comprising such powders, as well as individual components thereof. The disclosed powders may further be dispersed in selected suspension media to provide stabilized dispersions. Unlike prior art powders or dispersion for drug delivery, the present invention preferably employs novel techniques to reduce attractive forces between the particles. As such, the disclosed powders exhibit improved flowability and dispersibility while the disclosed dispersions exhibit reduced degradation by flocculation, sedimentation or creaming. As such, the disclosed preparations provide a highly flowable, dry powders that can be efficiently aerosolized, uniformly delivered and penetrate deeply in the lung or nasal passages. Furthermore, the perforated microstructures of the present invention result in surprisingly low throat deposition upon administration.

Please insert the following paragraphs at page 13, line 4:

The dispersions or powders may be used, for example, in conjunction with metered dose inhalers, dry powder inhalers, atomizers, nebulizers or liquid dose instillation (LDI) techniques to provide for effective drug delivery.

With regard to particularly preferred embodiments, the hollow and/or porous perforated microstructures substantially reduce attractive molecular forces, such as van de Waals forces, which dominate prior art powdered preparations and dispersions. In this respect, the powdered compositions typically have relatively low bulk densities which contribute to the flowability of the preparations while providing the desired characteristics for inhalation therapies. More particularly, the use of relatively low density perforated (or porous) microstructures or microparticulates significantly reduces attractive forces between the particles thereby lowering the shear forces and increasing the flowability of the resulting powders. The relatively low density of the perforated microstructures also provides for superior aerodynamic performance when used in inhalation therapy. When used in dispersions, the physical characteristics of the powders provide for the formation of stable preparations. Moreover, by selecting dispersion components in accordance with the teachings herein, interparticle attractive forces may further be reduced to provide formulations having enhanced stability.

With respect to the disclosed powders, the selected agent or bioactive agent, or agents, may be used as the sole structural component of the perforated microstructures. Conversely, the perforated microstructures may comprise one or more components (i.e. structural materials, surfactants, excipients, etc.) in addition to the incorporated agent. In particularly preferred embodiments, the suspended perforated microstructures will comprise relatively high concentrations of surfactant (greater than about 10% w/w) along with an incorporated bioactive agent(s). Finally, it should be appreciated that the particulate or perforated microstructure may be coated, linked or otherwise associated with an agent or bioactive agent in a non-integral manner. Whatever configuration is selected, it will be appreciated that any associated bioactive agent may be used in its natural form, or as one or more salts known in the art.

While the powders or stabilized dispersions of the present invention are particularly suitable for the pulmonary administration of bioactive agents, they may also be used for the localized or systemic administration of compounds to any location of the body. Accordingly, it should be emphasized that, in preferred embodiments, the formulations may be administered using a number of different routes including, but not limited to, the gastrointestinal tract, the respiratory tract, topically, intramuscularly, intraperitoneally, nasally, vaginally, rectally, aurally, orally or ocularly.

Please replace the paragraph at page 14, line 20 with the following:

Lipids, including phospholipids, from both natural and synthetic sources are particularly compatible with the present invention and may be used in varying concentrations to form the structural matrix. Generally compatible lipids comprise those that have a gel to liquid crystal phase transition greater than about 40° C. Preferably the incorporated lipids are relatively long chain (i.e. C_{16}-C_{22}) saturated lipids and more preferably comprise phospholipids. Exemplary phospholipids useful in the disclosed stabilized preparations comprise dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, long-chain saturated phosphatidylinositols, glycolipids, ganglioside GM1, sphingomyelin, phosphatidic acid, cardiolipin; lipids bearing polymer chains such as polyethylene glycol, chitin, hyaluronic acid, or polyvinylpyrrolidone; lipids bearing sulfonated mono-, di-, and polysaccharides; fatty acids such as palmitic acid, stearic acid, and oleic acid; cholesterol, cholesterol esters, and cholesterol hemisuccinate. Due to their excellent biocompatibility characteristics, phospholipids and combinations of phospholipids and poloxamers are particularly suitable for use in the pharmaceutical embodiments disclosed herein.

Please replace the paragraph at page 18, lines 1-16, with the following:

In addition to, or instead of, the components discussed above, the perforated microstructures will preferably comprise at least one active or bioactive agent. As used herein, the term "active agent" simply refers to a substance that enables the perforated microstructures to perform the desired function. Further, the term "active agent" shall be held inclusive of the term "bioactive agent" unless otherwise dictated by contextual restraints. As to the term "bioactive agent" it shall be held to comprise any substance that is used in connection with an application that is therapeutic or diagnostic in nature, such as methods for diagnosing the presence or absence of a disease in a patient, the diagnosis or treatment of a disease, and a condition or physiological abnormality in a patient. Particularly preferred bioactive agents for use in accordance with the invention include anti-allergics, peptides and proteins, pulmonary lung surfactants, bronchodilators and anti-inflammatory steroids for use in the treatment of respiratory disorders such as asthma by inhalation therapy. Preferred active agents for use in accordance with the present invention include pigments, dyes, inks, paints, detergents, food sweeteners, spices, adsorbants, antiinflammatories, antineoplastics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof. In preferred embodiments the bioactive agents comprise compounds which are to be administered systemically (i.e. to the systemic circulation of a patient) such as peptides, proteins or polynucleotides, absorbents, catalysts, nucleating agents, thickening agents, polymers, resins, insulators, fillers, fertilizers, phytohormones, insect pheromones, insect repellents, pet repellents, antifouling agents, pesticides, fungicides, disinfectants, perfumes, deodorants, and combinations of thereof. As will be disclosed in more detail below, the bioactive agent may be incorporated, blended in, coated on or otherwise associated with the perforated microstructure.

Please insert the following paragraphs at page 23, line 8:

With regard to the formation of the perforated microstructures it will be appreciated that, in preferred embodiments, the particles will be spray dried using commercially available equipment. In this regard the feed stock will preferably comprise a blowing agent that may be selected from fluorinated compounds and nonfluorinated oils. Preferably, the fluorinated compounds will have a boiling point of greater than about 60° C. Within the context of the instant invention the fluorinated blowing agent may be retained in the perforated microstructures to further increase the dispersibility of the resulting powder or improve the stability of dispersions incorporating the same. Further, nonfluorinated oils may be used to increase the solubility of selected bioactive agents (e.g. steroids) in the feed stock, resulting in increased concentrations of bioactive agents in the perforated microstructures.

The blowing agent may be dispersed in the carrier using techniques known in the art for the production of homogenous dispersions such a sonication, mechanical mixing or high pressure homogenization. Other methods contemplated for the dispersion of blowing agents in the feed solution include co-mixing of two fluids prior to atomization as described for double nebulization techniques. Of course, it will be appreciated that the atomizer can be customized to optimize the desired particle characteristics such as particle size. In special cases a double liquid nozzle may be employed. In another embodiment, the blowing agent may be dispersed by introducing the agent into the solution under elevated pressures such as in the case of nitrogen or carbon dioxide gas.